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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE GP1641

Our Ref: 1038-844 MISC

In re patent application	
No.	09/210,995
Applicant:	Sheena M. Loosmore et al
Title:	MULTI-COMPONENT VACCINE COMPRISING AT LEAST TWO ANTIGENS FROM HAEMOPHILUS INFLUENZAE TO PROTECT AGAINST DISEASE
Filed:	December 15, 1998
Group No.	1641
Examiner:	J. Hines

October 13, 2000

APPEAL BRIEF AND REQUEST FOR EXTENSION OF TIME

BY COURIER

The Commissioner of Patents
and Trademarks,
BOX AF,
Washington, D.C. 20231,
U.S.A.

Dear Sir:

1. Introduction

This Appeal Brief is submitted in support of applicant's appeal from the Final Rejection of claims 1 to 24. This Appeal Brief is submitted in triplicate.

2. Extension of Time

Petition is hereby made under the provisions of 37 CFR 1.136(a) for an extension of four months of the period for filing an Appeal Brief. The prescribed fee is enclosed.

10/17/2000 CNGUYEN 00000067 09210995
01 FC:120 310.00 OP
10/17/2000 CNGUYEN 00000067 09210995
02 FC:118 1380.00 OP

3. Real Party of Interest

The real party of interest in this application is Connaught Laboratories Limited by virtue of an Assignment from the inventors recorded at Reel/Frame 010239/0462 on December 15, 1998.

4. Related Appeals and Interferences

There are no other appeals or interferences known to appellant, appellant's legal representatives, or Assignee which will directly affect or be directly affected by or having a bearing on the Board's decision in the pending appeal.

5. Status of Claims

The application was filed with 24 claims. Claims 1 and 22 were amended in response to the first Office Action. The claims pending and appealed appear in an Appendix hereto.

6. Status of Amendments

Submitted simultaneously herewith is an Amendment after Final Action to correct a dependency error in claim 22.

7. Summary of Invention

The present invention is directed to an immunogenic composition for conferring protection in a host against disease caused by *Haemophilus influenzae*, including otitus media. The composition comprises at least two different antigens of *Haemophilus influenzae*, at least one of said antigens is an adhesin and the other of which is not an adhesin (page 5, lines 8 to 18).

The antigen which is an adhesin may be a high molecular weight (HMW) protein of a non-typeable strain of *Haemophilus influenzae*, particularly an HMW1 or HMW 2 protein of the non-typeable strain (page 5, lines 19 to 23).

The antigen which is not an adhesin may be a non-proteolytic heat shock protein of a strain of *Haemophilus influenzae*, which may be an analog of *Haemophilus influenzae* Hin47 protein having a protease activity which is less than about 10% of that of the natural Hin47 protease (page 5, line 24 to 31).

8. Issues

The sole issue for consideration is the rejection of claims 1 to 24 under 35 USC 103(a) as being unpatentable over Barenkamp et al in view of Loosmore et al.

9. Grouping of Claims

For the reasons outlined in the argument below, it is submitted that the claims do not stand or fall together.

10. Argument

(a) Background

Haemophilus influenzae is the cause of several serious human diseases, such as meningitis, epiglottitis, septicemia and otitis media. There are six serotypes of *H. influenzae*, designated a to f, that are identified by their capsular polysaccharide. *H. influenzae* type b (Hib) was a major cause of bacterial meningitis until the introduction of several Hib conjugate vaccines in the 1980's. Vaccines based upon *H. influenzae* type b capsular polysaccharide conjugated to diphtheria toxoid, tetanus toxoid, or *Neisseria meningitidis* outer membrane protein have been effective in reducing *H. influenzae* type b-induced meningitis. The other serotypes of *H. influenzae* are associated with invasive disease at low frequencies, although there appears to be an increase in the incidence of disease caused by these strains as the incidence of Hib disease declines. Non-encapsulated or non-typeable *H. influenzae* (NTHi) are also responsible for a wide range of human diseases including otitis media, epiglottitis, pneumonia and tracheobronchitis. The incidence of NTHi-induced disease has not been affected by the introduction of the Hib vaccines.

Otitis media is the most common illness of early childhood, with 60 to 70% of all children, of less than 2 years of age, experiencing between one and three ear infections. Chronic otitis media is responsible for hearing, speech and cognitive impairments in children. *H. influenzae* infections account for about 30% of the cases of acute otitis media and about 60% of chronic otitis media. In the United States alone, treatment of otitis media costs between 1 and 2 billion dollars per year for antibiotics and surgical procedures, such as tonsillectomies, adenoidectomies and insertion of tympanostomy tubes. It is estimated that an additional $30 billion is spent per annum on adjunct therapies, such as speech therapy and special education classes. Furthermore, many of the causative organisms of otitis media are becoming resistant to antibiotic treatment. An effective prophylactic vaccine against otitis media is thus desirable.

During natural infection by NTHi, surface-exposed outer membrane proteins that stimulate an antibody response are potentially important targets for bactericidal and/or protective antibodies and, therefore, potential vaccine candidates. Convalescent sera from children suffering from otitis media due to NTHi, contain antibodies to high molecular weight (HMW) proteins. About 70 to 75% of NTHi strains express the HMW proteins and most of these strains contain two gene clusters termed *hmw1ABC* and *hmw2ABC*. The HMWA proteins have been demonstrated to be adhesins mediating attachment to human epithelial cells. Immunization with a mixture of native HMW1A and HMW2A proteins has resulted in partial protection in the chinchilla intrabulla challenge model of otitis media.

Although the main goal of a prophylactic vaccine against *H. influenzae* disease, including otitis media, is to prevent the establishment of nasopharyngeal colonization by including an adhesin as immunogen, the HMW proteins are not present in encapsulated *H. influenzae* or in about 25% of NTHi strains. Therefore, a combination vaccine comprised of at least one adhesin molecule and an additional protective antigen found in all *H. influenzae* strains, will provide better coverage against disease and a broad spectrum of disease protection.

(b) Nature of the Present Invention

Having regard to the above Background, it would be desirable to provide efficacious combination vaccines comprising *H. influenzae* components containing selected relative amounts of selected antigens. The present invention provides an immunogenic composition for conferring protection in a host against disease caused by infection with *H. influenzae*, including otitis media.

The immunogenic composition comprises at least two different antigens of *H. influenzae*, at least one of which is an adhesin and the other of which is not an adhesin. Essential to the present invention, therefore, is a requirement for an immunogenic composition in which:

(i) at least two different antigens of *H. influenzae* are employed,

(ii) at least one of the antigens is an adhesin and the other antigen is not an adhesin.

In a specific embodiment of the invention, as claimed in claim 6, *H. influenzae* antigen which is an adhesin is a high molecular weight (HMW) protein of

a strain of non-typeable *H. influenzae* while the *H. influenzae* is not an adhesin is an analog of *H. influenzae* Hin47 protein having a decreased protease activity which is less than 10% of the natural Hin47.

Claim 7 recites that the HMW protein is present in an amount which enhances the immune response in the host to the Hin47 protein. Claim 8 recites that the HMW protein is present in the recited amount which the individual immunogenicity of the proteins in the composition are not impaired. The applicants data supports such results.

(c) Final Rejection

Claims 7 to 24 have been finally rejected under 35 USC 103(a) as being unpatentable over Barenkamp (WO 87/36914) in view of Loosmore. Barenkamp (WO 87/36914) teaches high molecular weight proteins of non-typeable *H. influenzae* identified as HMW1, HMW2, HMW3 and HMW4, which are characterized by molecular weight and sequence information. Loosmore et al teach an analog of *H. influenzae* Hin47 protein with reduced protease activity. It is submitted that these references lack any motivation to combine two different antigens of *H. influenzae*, one of which is an adhesin and the other of which is not an adhesin, (claim 1) namely a non-proteolytic heat shock protein of Loosmore et al with the HMW proteins of Barenkamp et al in an immunogenic composition (claim 6), particularly in quantities where the immunogenicity of the Hin47 protein is improved by the HMW protein (claim 7) and in which the individual immunogenicities are not impaired (claim 8).

In the Final Action, the Examiner states:

> "Applicants argues that Barenkamp et al., (WO 97/36,914) provides no suggestion that the High Molecular Weight (HMW) antigens can be used in conjunction with the recited antigens. However, Barenkamp et al., teaches that the HMW protein can be linked to an antigen, hapten or polysaccharide for eliciting an immune response to the antigen, hapten or polysaccharide (page 6 lines 2-5)."

This passage in Barenkamp et al refers to linking the HMW protein to materials with low or no immune response for the purpose of improving that response. It is well known that carrier proteins can be used for this purpose. This disclosure is

irrelevant to combining antigens which are already highly immunogenic in an immunogenic composition, as in the present invention.

The Examiner goes on to state:

> "Further, Barenkamp et al., teaches that targeting molecules used in combination immunogenic compositions can include fragments of bacterial toxins (page 6 lines 33-34)."

This passage of Barenkamp et al is dealing with formulation of an immunogenic composition containing the HMW protein in combination with a targeting molecule for delivery to specific cells of the immune system. There is no suggestion that the mutant Hin47 protein is a targeting vehicle and hence this passage of Barenkamp is irrelevant.

The Examiner goes on to state, in the Office Action:

> "The immunogenic composition may also comprise at least one other immunogenic or immunostimulating material and at least one adjuvant"

The Examiner is correct that such statement appears in lines 1 to 4 on page 7. However, that is far from any specific teaching to combine mutant Hin47 protein with HMW protein in an immunogenic composition. There is no suggestion at all that the other immunogenic material should be from *H. influenzae*.

The Examiner also states:

> "and teaches complexing additional components to the antigenic composition to enhance immune response including herpes simplex virus vaccine, pseudorabies virus vaccine, tetanus toxoid, poliomyelitis virus vaccine and hepatitis B virus antigen and others."

As has been pointed out previously in response to a similar assertion in the first Office Action, this is an incorrect statement. It is not known why the Examiner persists in this incorrect notion having regard to applicants comments. As previously pointed out in response to the first Office Action, the references to herpes simplex virus vaccine and pseudorabies virus vaccine (page 24, ll. 19 to 21) are made in the context of reporting work done by Lockhoff (USP 4,855,283) using glycolipid analogs as adjuvants, suggesting that such analogs could be used in the HMW containing immunogenic compositions as adjuvants. There is absolutely no suggestion in Barenkamp of "complexing additional components to the immunogenic composition" in the form of herpes simplex virus (HSV), but rather the possibility of

using glycolipid analogs as an adjuvant for the HMW protein is discussed, since it has been used with HSV.

The references to tetanus toxoid and poliomyelitis virus vaccine (page 24, ll. 28 to 30) are in the context of reporting work performed by Maloney (USP 4,258,029) using octadecyl tyrosine hydrochloride (OTH) as adjuvants, suggesting that OTH could be used as an adjuvant in the HMW protein containing immunogenic compositions. There is absolutely no suggestion in Barenkamp of combining tetanus toxoid and/or polio vaccine with HMW in an immunogenic composition.

Similarly, the reference to hepatitis B virus antigen (page 24, ll. 31 to 32) is in the context of reporting work performed by Nixon-George et al (ref. 30) using octadecyl esters of aromatic amino acids as adjuvants, suggesting that such material would be used as adjuvants in the HMW protein containing immunogenic compositions. There is absolutely no suggestion in Barenkamp of combining hepatitis B virus antigen with HMW in an immunogenic composition.

It is submitted that it is entirely out of context to suggest, as the Examiner does in the above quotations from the Final Action, that, on the basis of these disclosures, HMW protein would be combined with any one or a combination of herpes simplex virus vaccine, pseudorabies virus vaccine, tetanus toxoid, poliomyelitis virus vaccine and hepatitis B virus antigen in an immunogenic composition. The passages in question in Barenkamp et al are discussing certain materials which may be used as adjuvants in the HMW-containing immunogenic composition, because they have been used in other vaccine formulations with the recited vaccine materials.

The Examiner next states in the Final action:

> "Barenkamp et al., combined vaccines can contain material from various pathogens or from various strains of the same pathogen, or from combinations of various pathogens (page 22 lines 5-8). Barenkamp et al., specifically teaches that vaccines which contain antigenic material of several pathogens are combined vaccines and also belong to the present invention (page 22 lines 5-8)."

The passage in question describes the possibility of having vaccines containing

> "... materials from various pathogens or from various strains of the same pathogen, or from combinations of various pathogens."

This passage is but a statement of the possibility of combining other antigens with the HMW protein in a vaccine composition. This passage contains no suggestion to select the mutant Hin47 protein for combination with HMW protein.

In addition, this passage contains no disclosure suggesting combination of an antigen of *H. influenzae* which is an adhesin, such as the HMW protein described by Barenkamp, with another antigen of *H. influenzae* which is not an adhesin, as required by claim 1. There is no motivation provided by the references to make the combination urged by the Examiner.

Based on this paucity of disclosure, at least part of which has clearly been misinterpreted by the Examiner as noted above, the Examiner concludes in the Final Action:

> "Therefore it would have been obvious at the time of applicant's invention to have an immunogenic composition to confer protection against *Haemophilus influenza* comprising at least two different antigens, where one is a high molecular weight adhesin protein, HMW1 or HMW2, since Barenkamp et al. (WO 97/36,914), teaches that adhesin proteins are potentially important protective antigens which should comprise one component of a multi-component non-typeable *H. influenzae* vaccine and the other component as taught by Loosmore et al., is an analog of Hin47 because Hin47 is a non-proteolytic heat shock protein which substantially reduced in proteolytic activity and can be used as an antigen and be included in other immunogenic preparations."

There is no indication in Barenkamp et al that:

> "Barenkamp et al ... teaches that adhesin proteins are potentially important protective antigens which should comprise one component of a multi-component non-typeable *H. influenzae* vaccine" (emphasis added)

as asserted by the Examiner in the Final Action.

Where is the statement in Barenkamp et al to provide a multi-component non-typeable *H. influenzae* vaccine? Clearly there is none. In addition, there is no indication in Barenkamp et al that:

> "Barenkamp et al ... teaches ... the other component as taught by Loosmore et al is an analog of Hin47"

Where is the statement in Barenkamp et al that, in the non-disclosed multi-component non-typeable *H. influenzae* vaccine, a non-proteolytic analog of Hin47

which is not an adhesin should be selected for such multi-component vaccine? Clearly there is none. The combination of cited prior art lacks any motivation whatsoever to select the mutant Hin47 protein of Loosmore et al and combine it with the HMW protein.

In addition, there is a clear lack of any motivation whatsoever to provide a composition comprising an HMW protein and a non-proteolytic analog of Hin47 in which the quantity of HMW protein present enhances the immunogenicity of the already highly immunogenic non-proteolytic analog of Hin47 protein, as recited in claim 7.

In addition, an important consideration when combining antigens in an immunogenic composition, is the possibility of impairing or adversely affecting the respective immunogenicities. In fact, applicants data showed antigenic interference for certain doses and an enhancing effect under other doses (see page 12, line 13 to page 13, line 9). In addition, at dose levels where the HMW and Hin47 proteins did not impair their respective immunogenicities, formulating such components with DTP-polio-PRP-T vaccine did not result in any significant synergistic or suppressive effect on the additional antigens (see page 14, lines 10 to 23). Such results could not have been predicted in advance from the information provided in Barenkamp et al and Loosmore et al.

Accordingly, a person skilled in the art would not know ahead of time, assuming he were to select the non-proteolytic analog of Hin47 to combine with HMW protein, a motivation which, it is submitted, is completely lacking in the art, whether or not the proteins were combinable into an effective multi-component immunogenic composition.

In the Final Action, the Examiner attempts to address the lack of motivation to select mutant Hin47 to combine with HMW protein in an immunogenic composition and further states:

> "Both Barenkamp et al. (WO 97/36,914), and Loosmore et al., teach the use of adjuvants, the addition of other additional antigenic components and methods for immunizing a host against disease caused by an infection with *H. influenzae* comprising administration of the composition."

The teachings of Barenkamp et al with respect to "other antigenic component" has been discussed above. Adjuvants are commonly used in immunogenic compositions intended for vaccine use and hence their recitation in Barenkamp et al and Loosmore et al is hardly surprising, but totally irrelevant to any motivation to select a non-proteolytic analog of Hin47, as described by Loosmore et al, to combine with the HMW protein to provide a multi-component immunogenic composition as defined by applicants claims.

In the Final Action, the Examiner points to no specific teaching of Loosmore et al to support the suggestion that Loosmore et al teach the addition of an additional antigenic material to the HMW antigen. However, the following passages may be found in Loosmore et al:

> "The immunogenic compositions of the invention may further comprise at least one other immunogenic or immunostimulating material such as an adjuvant" (col. 3, ll. 63 to 66)
>
> "Vaccines which contain antigenic material of several pathogens are combined vaccines and also belong to the present invention. Such combined vaccines contain ... material from various pathogens or from various strains of the same pathogen, or combinations of various pathogens" (col. 9, ll. 10 to 19).

It is assumed that these are the passages on which the Examiner relies. However, it can be seen that they are no more relevant than the vague generalities contained in Barenkamp et al with respect to additional components. Yet, on the basis of these teachings, the Examiner asserts in the Final Action:

> "Thus, applicants argument that because is no suggestion to combine a HMW protein and the Hin47 because neither protein is specifically recited is not persuasive."

It is again urged that there is no motivation provided from the disclosure of Barenkamp et al to select the non-proteolytic analog of Hin47 protein, as described by Loosmore et al from the myriad of possibilities for "additional antigen components" and combine that specifically-selected *Haemophilus influenzae* antigen with the HMW protein. In addition, there is no motivation to select the non-proteolytic analog of Hin47 protein for the purpose that the applicants make the selection.

Nor does the combination of prior art suggest combining two different antigen of *H. influenzae* into an immunogenic composition, one of which is an adhesin and the other of which is not an adhesin, as required by claim 1.

The Examiner concludes in the Final Action:

> "It would have been obvious at the time of applicant's invention to have an immunogenic composition which confers protection against *Haemophilus influenzae* comprising at least two different antigens, where at least one of the antigens is an adhesin and the other antigen is not an adhesin as taught by Barenkamp et al. (WO 97/36,914), in view of Loosmore et al."

It is once again pointed out that there is no specific teaching in Barenkamp et al to provide an immunogenic composition which confers protection against *Haemophilus influenzae* comprising at least two different antigens, where at least one of the antigens is an adhesin and the other antigen is not an adhesin, no matter how hard the Examiner may wish it were so.

The Examiner goes on in the Final Action:

> "Loosmore et al., teaches that adhesin proteins are potentially important protective antigens which should comprise other immunostimulating components; the Hin47 antigen is immunogenic because it stimulates an immune response, can confer protection against diseases caused by a bacterial pathogen, including *Haemophilus influenzae;* and may immunogenic composition may further comprise at least one other immunogenic or immunostimulating material."

These disclosures of Loosmore et al provide no motivation whatsoever to select a non-proteolytic Hin47 which is not an adhesin for combination with the HMW protein of Barenkamp et al.

The Examiner's rejection does not take into account the reason why applicants combine these two proteins, as set forth in the Background to the Invention section of the specification. The applicants are striving to develop a vaccine intended to be effective against otitis media caused by *Haemophilus influenzae*.

Barenkamp et al had isolated and characterized the HMW protein, which is a high molecular weight outer membrane protein of non-typeable strains of *Haemophilus influenzae*. These proteins were found to be adhesins and prevent

establishment of nasopharyngeal colonization by *H. influenzae*. However, applicants have found that the HMW are not present in all encapsulated (non-typeable) strains of *H. influenzae* but rather in about 75% of NTHi strains. Accordingly, to provide a better coverage against disease and a broad spectrum of disease protection, it is desirable to provide an additional protective antigen found in all *H. influenzae* strains. The latter protein is Hin47 protein employed herein, in the form of a non-proteolytic analog.

In response to a request for reconsideration of the Final Action, the Examiner issued an Advisory Action dated June 7, 2000, in which the Examiner indicated that applicants request was denied stating:

"Applicant argues features not claimed . . ."

It is submitted that the focus of the applicant's arguments mirror the arguments presented by the Examiner and that all features discussed in the context of such argument are contained in the claims.

The Examiner also supplemented the Advisory Action with a "Response to Arguments". In this regard, the Examiner states:

> "In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e. the Hin47 protein has decreased protease activity) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims."

The feature that the Hin47 protein employed is one having decreased protease activity is specifically claimed. For example, claim 5 recites:

> ". . . an analog of *Haemophilus influenzae* Hin47 protein having a decreased protease activity which is less than about 10% of that of natural Hin47 protein." (emphasis added).

Precisely the same language is used in claim 6. Accordingly, it is not seen on what basis the Examiner can assert that this feature "upon which applicant relies" is not recited in the claims.

In the Advisory Action, the Examiner further states:

> "In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness' can only be established by combining or modifying the teachings of the

> prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the reverences themselves or in the knowledge generally available to one of ordinary shill in the art. In this case, it would have been obvious at the time of applicant's invention to have an immunogenic composition to confer protection against *Haemophilus influenzae* comprising at least two different antigens, where one is a high molecular weight adhesin protein, HMW1 or HMW2, since Barenkamp et al. (WO 97/36914), teaches that adhesin proteins are potentially important protective antigens which should comprise one component of a multi-component non-typeable *Haemophilus influenzae* vaccine and the other component as taught by Loosemore et al., is an analog of Hin47 because Hin47 is non-proteolytic heat shock protein which substantially reduced in proteolytic activity and ca be used as an antigen and be included in other immunogenic preparations."

As pointed out in detail above, the Examiner is mistaken. While it is correct for the Examiner to state that adhesin proteins, specifically to HMW1 and HMW2 proteins of Barenkamp (WO 97/36914), are potentially protective antignes. Barenkamp does not recite that such adhesin protein "should" comprise one component of a multi-component non-typeable *Haemophilus influenzae* vaccine. As pointed out previously, the only mention of additional materials in Barenkamp is on page 7, lines 1 to 4:

> "The immunogenic compositions of the invention (including vaccines) may {not should} further comprise at least one other immunogenic . . . . material."

There is nothing in this passage which indicates that the HMW protein "should" be combined with the non-proteolytic analog of Hin47 protein. While the Loosmore et al reference, as noted above, refers to the possibility of combining the analog antigen with other immunogenic materials, there is no suggestion that such immunogenic material be the HMW protein of Barenkamp.

The Examiner, therefore, is in error in stating that Barenkamp (WO 97/36914) teaches that adhesin proteins "should comprise" one component of a multi-component non-typeable *Haemophilus influenzae* vaccine and the other component is non-proteolytic analog of Hin47, as taught by Loosmore et al. The prior art combination cited by the Examiner lacks any motivation to make the

combination urged by the Examiner (absent, of course, the hindsight of the present invention).

For all the above reasons, it is submitted that the Examiner is in error is rejecting claims 1 to 24 under 35 USC 103(a) as being unpatentable over Barenkamp (WO 97/36914) in view of Loosmore et al.

(d) Specific Claims

- Claim 1 defines an immunogenic composition at least two different antigens of *Haemophilus influenzae*, at least one of which is an adhesin and the other of which is not an adhesin. The manner of distinction of this claim over the cited combination of prior art has been discussed in detail above and requires no further discussion.
- Claims 2 and 3 recite that the adhesin antigen is the HMW protein and this is disclosed in Barenkamp.
- Claims 4 and 5 recite that the non-adhesin antigen is the non-proteolytic analog of Hin47 of Loosmore et al. However, as has already been demonstrated, claim 1 is patentable over the applied combination of prior art. These claims are dependent, directly and indirectly, on claim 1 and hence these claims are patentable over the applied combination of prior art.
- Claim 6 is an independent claim and defines an immunogenic composition comprising an analog of *Haemophilus influenzae* Hin47 protein having a decreased protease activity which is less than about 10% of the natural Hin47 protein and a high molecular weight (HMW) protein of a strain of non-typeable *Haemophilus influenzae*. Although Loosemore et al disclosed the Hin47 analog and Barenkamp dislcoses that HMW protein, as argued above, there is no motivation in the prior art to make the claimed specific combination of antigens in an immunogenic composition. Accordingly, claim 6 is separately patentable over the applied combination of prior art, independent of the patentability of claim 1.
- Claim 7 is dependent on claim 6 and recites that the HMW protein is present in the composition in an amount which enhances the immune

response in the host to the Hin47 protein. Not only is there no motivation in the prior art to combine the HMW protein with the Hin47 analog protein, but there is no disclosure or suggestion to combine the antigen in amounts which result in enhancement of the immune response to the Hin47 analog, since it is a weaker immunogen. For all these reasons, it is submitted that claim 7 is separately patentable over the combination of prior art, irrespective of the patentability of claim 6.

- Claim 8 is dependent on claim 7 and recites that the HMW protein is present in the immune-response enhancing amount while the individual immunogenicity of the proteins are not impaired. Not only is there no motivation in the prior art to combine the HMW protein with Hin47 analog protein in the Hin47 analog immune-response enhancing amount, as recited in claim 7, but also the cited combination of prior art fails to disclose or suggest combining the proteins in amounts which do not impair the respective immunengicities. Accordingly, it is submitted that claim 8 is separately patentable over the applied combination of prior art, irrespective of the patentability of claims 6 and 7.
- Claim 9 to 14 are dependent, directly or indirectly, on claim 6 and recite specific features of the Hin47 analog, such features being disclosed in Loosmore et al. However, as discussed above, claim 6 is patentable over the applied combination of prior art and, for this reason, claims 9 to 14 are patentable over the applied combination of prior art.
- Claim 15 to 17 are dependent on claim 8 and recite features of the HMW protein certain of which are found in Barenkamp. However, it has been demonstrated above that claim 8 is separately patentable over the applied combination of prior art. Since claims 15 to 17 are dependent on claim 8, those claims are patentable over the prior art along with claim 8.
- Claim 18 and 19 recite that the composition of claim 6 may further comprise an adjuvant, which may be aluminum hydroxide or aluminum phosphate (claim 19). It is conceded that it is well known to formulate immunogenic compositions with adjuvants and that aluminum

hydroxide and aluminum phosphate (collectively known as "alum") are known adjuvants. However, it has been demonstrated above that claim 6 is patentable over the prior art and hence claims 18 and 19 are patentable over the applied art along with claim 6.

- Claim 20 is dependent on claim 6 and recites specific proportions of the Hin47 protein analog and the HMW protein. Not only does the cited prior art not disclose or suggest the specific combination of antigens recited in claim 6, but also the cited combination of prior art fails to disclose or suggest combining these antigens in the specific proportions disclosed in claim 20. Accordingly, it is submitted that claim 20 is separately patentable over the applied art, irrespective of the patentability of claim 6.
- Claim 21 is dependent on claim 6 and recites that the composition further comprises at least one additional antigen component for conferring protection against infection caused by another pathogen. As noted earlier, at least both Barenkamp and Loosmore et la have disclosure concerning formulating the respective antigen with other immunogenic material. However, there is no disclosure or suggestion in the cited combination of prior art, to combine two specific antigens of *Haemophilus influenzae* with at least one additional antigenic component for conferring protection against infection caused by another pathogen, as reacted in claim 21. Accordingly, irrespective of the patentability of claim 6, it is considered that claim 21 is separately patentable over the cited combination of prior art.
- Claim 22 currently incorrectly refers to claim 6 but the Amendment after Final Action referred to above corrects the error and makes claim 22 dependent on claim 21. Claim 22 and 23 recite specific material which may comprise the additional antigenic component of claim 21. While these claimed materials are all known to be antigens, there is no specific disclosure in Barencamlp or Loosmore, nor in the combination of prior art, which suggests combining the specific materials with the specific combination of two *Haemophilus influenzae* antigens of claim

6. Accordingly, it is submitted that claims 22 and 23 are separately patentable over the prior art, irrespective of the patentability of claims 6 and 21.

- Claim 24 defines a method of immunizing a host against disease caused by infection with *Haemophilus influenzae*, including otitus media, which comprises administering to the host an immunoefficient amount of the composition of claim 1 or 6. The patentability of claim 1 and claim 6 over the cited combination of prior art has been demonstrated above. For this reason, it is submitted that claim 24 is patentable over the applied combination of prior art.

Having regard to the above discussion, it is submitted that all pending claims are patentable over the applied art.

11. Summary

Having regard to the above detailed discussion, it is submitted that the Examiner is in error in rejecting claim 1 to 24 as being unpatentable and hence the rejection thereof under 35 USC 103(a) as being unpatentable over the combination of Barenkamp (WO 97/36914) in view of Loosmore et al, should be REVERSED.

Respectfully submitted,

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APPENDIX

CLAIMS APPEALED

1. An immunogenic composition for conferring protection in a host against disease caused by *Haemophilus influenzae*, comprising:

at least two different antigens of *Haemophilus influenzae*, at least one of which antigens is an adhesin and the other of which antigen is not an adhesin.

2. The immunogenic composition of claim 1 wherein said antigen which is an adhesin is a high molecular weight (HMW) protein of a non-typeable strain of *Haemophilus influenzae*.

3. The immunogenic composition of claim 2 wherein said HMW protein is a HMW1 or HMW2 protein of the non-typeable strain of *Haemophilus influenzae*.

4. The immunogenic composition of claim 1 wherein the antigen of *Haemophilus influenzae* which is not an adhesin is a non-proteolytic heat shock protein of a strain of *Haemophilus influenzae*.

5. The immunogenic composition of claim 4 wherein the non-proteolytic heat shock protein of a strain of *Haemophilus influenzae* is an analog of *Haemophilus influenzae* Hin47 protein having a decreased protease activity which is less than about 10% of that of natural Hin47 protein.

6. An immunogenic composition for conferring protection in a host against disease caused by *Haemophilus influenzae*, which comprises:

an analog of *Haemophilus influenzae* Hin47 protein having a decreased protease activity which is less than about 10% of that of natural Hin47 protein, and

a high molecular weight (HMW) protein of a strain of non-typeable *Haemophilus influenzae*.

7. The composition of claim 6 wherein said HMW protein is present in said composition in an amount which enhances the immune response in the host to the Hin47 protein.

8. The composition of claim 7 wherein said HMW protein is present in the said amount while the individual immunogenicities of the proteins in the composition is not impaired.

9. The composition of claim 6 wherein said analog of Hin47 protein is one in which at least one amino acid of the natural Hin47 protein contributing to protease activity has been deleted or replaced by a different amino acid and which has substantially the same immunogenic properties as natural Hin47 protein.

10. The composition of claim 9 wherein said at least one amino acid is selected from the group consisting of amino acids 91, 121 and 195 to 201 of natural Hin47 protein.

11. The composition of claim 10 wherein Serine-197 is replaced by alanine.

12. The composition of claim 10 wherein Histidine-91 is replaced by alanine, lysine or arginine.

13. The composition of claim 12 wherein Histidine-91 is replaced alanine.

14. The composition of claim 10 wherein Asp-121 is replaced by alanine.

15. The composition of claim 8 wherein said HMW protein is an HMW1 or HMW2 protein of a non-typeable strain of *Haemophilus influenzae*.

16. The composition of claim 15 wherein the HMW1 and HMW2 proteins are produced recombinantly.

17. The composition of claim 15 wherein said HMW1 and HMW2 proteins are derived from the respective strain of non-typeable *Haemophilus influenzae* and possess respective molecular weights as set forth in the following Table:

Molecular Weight(kDa)	Non-typeable *H. influenzae* Strain					
	12	JoyC	K21	LCDC2	PMH1	15
Mature Protein: HMW1	125	125.9	104.4	114.0	102.4	103.5
HMW2	120	100.9		111.7	103.9	121.9

18. The composition of claim 6 further comprising an adjuvant.

19. The composition of claim 18 wherein said adjuvant is aluminum hydroxide or aluminum phosphate.

20. The composition of claim 6 comprising

about 25 to about 100 μg of the Hin47 protein analog, and

about 25 to about 100 μg of the HMW protein.

21. The composition of claim 6 further comprising at least one additional antigenic component for conferring protection against infection caused by another pathogen.

22. The composition of claim 6 wherein said at least one additional antigenic component is selected from the group consisting of diphtheria toxoid, tetanus toxoid, pertussis antigens, non-virulent poliovirus and a conjugate of a tetanus or diphtheria toxoid and a capsular polysaccharide of *Haemophilus influenzae*.

23. The composition of claim 22 wherein said pertussis antigens are selected from the group consisting of pertussis toxoid, filamentous hemagglutinin, pertactin and agglutinogens.

24. A method of immunizing a host against disease caused by infection with *Haemophilus influenzae*, including otitis media, which comprises administering to the host an immunoeffective amount of a composition as claimed in claim 1 or 6.